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10/535,307	12/07/2005	Andrew N Margioris	Q87992	3693

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EXAMINER	
BORGEEST, CHRISTINA M	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/535,307	MARGIORIS ET AL.	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *1-3,11 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-10,13 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Applicants' amendment filed 22 May 2008 is acknowledged. Claims 1, 3, 4, 6, 11, 12 and 13 are amended. Claims 1-3, 11 and 12 are withdrawn from consideration and claims 4-10, 13 and 14 are under examination.

Objections withdrawn

The objection to claims 4 and 13 objected to for informalities as set forth at p. 2 of the Office action mailed 22 January 2008 is withdrawn in response to Applicants' amendment of these claims to write out the full terms followed by abbreviations in parentheses.

Rejections Maintained

Claim Rejections - 35 USC § 112, first paragraph—Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 4-10, 13-14 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pharmaceutical compositions and kits comprising CRH-R2 agonists and CRH-R1 antagonists that are known in the art, does not reasonably provide enablement for the claims as broadly recited, as set forth

at pages 3-5 of the Office action mailed 22 January 2008 is maintained for reasons of record and the following.

Applicants argue at p. 9, 1st and 2nd paragraphs that claim 4 has been amended to recite that the CRH-R1 antagonists and/or CRH-R2 agonists directly modify the response of monocyte/macrophage cell activation, proliferation, differentiation or apoptosis and that claim 13 recite a kit for the treatment of an inflammatory disease or condition wherein the CRH-R1 antagonists and/or CRH-R2 agonists directly modify the response of monocyte/macrophage cell activation, proliferation, differentiation or apoptosis.

This argument has been fully considered but is not found persuasive. Applicants have added an activity limitation in the complete absence of any structural limitation. This unfairly limits the skilled artisan from undertaking research in this area, since any product, known or unknown, that acts as either a CRH-R1 antagonist or CRH-R2 agonist that modifies a response of monocyte/macrophage cell activation, proliferation, differentiation or apoptosis would be protected by such a patent claim. In effect, the skilled artisan would be required to discover the pharmaceutical compositions on behalf of the inventors, but would be then barred from pursing any research in the area.

Applicants argue at p. 9, 3rd paragraph that the specification teaches that in vivo and in vitro, human experiment models have been used to demonstrate the regulatory role of the CRH system of monocyte/macrophages and that CRH-R1 antagonists and/or CRH-R2 agonists ameliorate the inflammatory response.

This argument has been fully considered but is not found persuasive. The claimed products are pharmaceutical compositions for inflammatory diseases such as chronic inflammatory bowel disease, idiopathic inflammatory disorder, inflammatory disorders of connective tissues, inflammatory demyelinating polyneuropathies, inflammatory, myopathies, inflammatory diseases of joints including bursitis, the fibromyalgia syndrome and/or inflammatory diseases of upper gastrointestinal tract.

thus the skilled artisan must undertake studies to determine whether the CRH-R1 antagonists and/or CRH-R2 agonists are capable of treating the myriad diseases contemplated by the specification. Although Applicants put forth a mechanism of action in the specification, namely that CRH-R1 antagonists and/or CRH-R2 agonists ameliorate the inflammatory response, this does not necessarily mean that every that CRH-R1 antagonist and/or CRH-R2 agonist yet to be discovered will be capable of treating all inflammatory diseases. A great burden is placed upon the skilled artisan to discover agents and test their efficacy in disease treatment on behalf of the inventors. Because the claims are so broad, the claims as currently written would provide protection against CRH-R1 antagonists and/or CRH-R2 agonists yet to be discovered, thus preventing the skilled artisan from undertaking research in this area.

Applicants argue at p. 10, 1st paragraph that the skilled artisan could envision manufacturing CRH-R1 antagonists and/or CRH-R2 agonists.

This argument has been fully considered but is not found persuasive. The major issue is breadth of the claims, which provide no structural limitations on said CRH-R1 antagonists and/or CRH-R2 agonists. The skilled artisan would be barred from research into this area because the claims are single means claims. Single means claims are those that cover every conceivable means for achieving the stated purpose. When claims depend on a recited property (in this case, merely CRH-R1 antagonists and/or CRH-R2 agonists) a fact situation comparable to Hyatt is possible, where the claim covers every conceivable structure for achieving the stated property (modification of the response of monocyte/macrophage cell activation, proliferation, differentiation or apoptosis) while the specification discloses at most only those known to the inventor.

See MPEP 2164.08(a). Furthermore, because the CRH-R1 antagonists and/or CRH-R2 agonists are claimed as pharmaceutical compositions, the skilled artisan would have to undertake research to determine which CRH-R1 antagonists and/or CRH-R2 agonists were effective at treating inflammatory diseases.

Applicants argue at p. 10, 2nd paragraph that the specification discloses three examples of compounds usable in the method of the invention having the claimed features, namely synthetic antalarmin, CRH and endogenous urocortin and that assays to discover additional CRH-R1 antagonists and/or CRH-R2 agonists are disclosed in the specification.

This argument has been fully considered, but is not found persuasive. Again, the major issue is breadth of the claims, which provide no structural limitations on said CRH-R1 antagonists and/or CRH-R2 agonists. The Examiner's discussion in the preceding paragraph is hereby incorporated.

Applicants argue at p. 11, whole page, that the skill in the art is very high and that "all known endogenous as well as synthetic agonists and antagonists of CRH receptors are classified according to their resemblance to the prototypes of CRH and urocortin".

This argument has been fully considered, but is not found persuasive. While the Examiner takes no issue with the assertion that the skill in the art is high, it is but one factor that must be considered when deciding whether claims are enabled by the disclosure. First, the claims encompass unknown as well as known CRH-R1 antagonists and/or CRH-R2 agonists. In the absence of any structural limitation the skilled artisan must undertake a large quantity of experimentation necessary to discover all the CRH-R2 agonists and CRH-R1 antagonists encompassed by the claims and test their usefulness at inflammatory disease treatment. Furthermore, the specification provides only three examples of CRH-R1 antagonists and/or CRH-R2 agonists, two of

which are endogenous (i.e., not "synthetic"), thus there is a lack of direction/guidance presented in the specification regarding and the absence of working examples directed to all of the agents encompassed by the claims. Finally, there is an issue with the breadth of the claims which fail to recite limitations on CRH-R2 agonists and CRH-R1 antagonists, which would require the person of skill in the art to undergo a discovery process to determine the agents encompassed by the claims, and furthermore limit their ability to research this area, since the claims as written would provide protection for undiscovered CRH-R1 antagonists and/or CRH-R2 agonists. In effect, the skilled artisan would be required to discover and test the pharmaceutical compositions encompassed by the claims.

Applicants argue at p. 12, 1st full paragraph that the assertion that there are limitless structural possibilities to the compounds of the invention is irrelevant to the determination to whether one skilled in the art can make and or use the invention.

This argument has been fully considered but is not found persuasive. In fact, because of the breadth of the claims and the complete lack of structural limitation, the skilled artisan could never fully discover each an every CRH-R1 antagonist and/or CRH-R2 agonist encompassed by the claims. Furthermore, the public would be unfairly restricted in researching this area since the claims, as written, would provide patent protection for each and every new discovery of a CRH-R1 antagonist and/or CRH-R2 agonist made by the skilled artisan.

Claim Rejections - 35 USC § 112, first paragraph—Written Description

The rejection of claims 4-10 and 13-14 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as set forth at pages 5-7 of the

Office action mailed 22 January 2008 is maintained for reasons of record and the following.

Applicants presented the same arguments for the rejection under Written Description as those presented for the rejection under Enablement, and they are reiterated below:

Applicants argue at p. 9, 1st and 2nd paragraphs that claim 4 has been amended to recite that the CRH-R1 antagonists and/or CRH-R2 agonists directly modify the response of monocyte/macrophage cell activation, proliferation, differentiation or apoptosis and that claim 13 recite a kit for the treatment of an inflammatory disease or condition wherein the CRH-R1 antagonists and/or CRH-R2 agonists directly modify the response of monocyte/macrophage cell activation, proliferation, differentiation or apoptosis.

Applicants argue at p. 9, 3rd paragraph that the specification teaches that in vivo and in vitro, human experiment models have been used to demonstrate the regulatory role of the CRH system of monocyte/macrophages and that CRH-R1 antagonists and/or CRH-R2 agonists ameliorate the inflammatory response.

Applicants argue at p. 10, 1st paragraph that the skilled artisan could envision manufacturing CRH-R1 antagonists and/or CRH-R2 agonists.

Applicants argue at p. 10, 2nd paragraph that the specification discloses three examples of compounds usable in the method of the invention having the claimed features, namely synthetic antalarmin, CRH and endogenous urocortin and that assays to discover additional CRH-R1 antagonists and/or CRH-R2 agonists are disclosed in the specification.

Applicants argue at p. 11, whole page, that the skill in the art is very high and that "all known endogenous as well as synthetic agonists and antagonists of CRH receptors are classified according to their resemblance to the prototypes of CRH and urocortin".

Applicants argue at p. 12, 1st full paragraph that the assertion that there are limitless structural possibilities to the compounds of the invention is irrelevant to the determination to whether one skilled in the art can make and or use the invention.

These arguments have been fully considered but are not found persuasive.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus, and in the instant case, the specification discloses only one synthetic and two endogenous CRH-R1 antagonists and/or CRH-R2 agonists. The claims have no structural limitations and encompass all CRH-R1 antagonists and/or CRH-R2 agonists, both known and unknown. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a recitation of a CRH-R2 agonist or CRH-R1 antagonist. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus, which encompasses undiscovered CRH-R2 agonists or CRH-R1 antagonists.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). It is clear from paragraphs [0020] – [0022] of the instant specification that Applicants are not in possession of the claimed genus.

With the exception of CRH-R2 agonists and CRH-R1 antagonists known in the art, the skilled artisan cannot envision the detailed chemical structure of the encompassed agents, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. ***Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it,*** as is disclosed at paragraphs [0020] - [0022] of the specification**.** The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated CRH-R2 agonists and CRH-R1 antagonists known and documented in the art (in addition to antalarmin), but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 4-10 and 13-14 under 35 U.S.C. 102(b) as being anticipated by Webster et al. (Endocrinol. 1996; 137: 5747-5750) as set forth at pages 7-9 of the Office action mailed 22 January 2008 is maintained for reasons of record and the following.

Applicants argue at p. 12, last paragraph that although Webster et al. teach that antalarmin reduces the severity of inflammation, they do not describe the cellular and signaling mechanisms of this effect.

This argument has been fully considered but is not found persuasive. The claims are drawn to a pharmaceutical composition, which is a ***product***. See In re Papesch, 315 F.2d 381, 391, 137 USPQ 43, 51: "From the standpoint of patent law, a compound and all its properties are inseparable." Note that the recitation, "directly modifying the response of monocyte/macrophage cell activation, proliferation, differentiation or apoptosis" is given little patentable weight for the purpose of evaluating the prior art, because it does not further limit ***the structure of the product***. Because the product taught by Webster and colleagues is identical to that taught in the instant application, the prior art product must, by definition, have the same ability to directly modify the response of monocyte/macrophage cell activation, proliferation, differentiation or apoptosis. It is not necessary for Webster et al. to have disclosed the mechanism of action, as the claims are drawn to products and Webster et al. disclose the products and their usefulness as an anti-inflammatory (see for example, abstract; p. 5750, left column, last 2 paragraphs), thus the usage taught by Webster and colleagues is

consistent with a pharmaceutical composition. Finally, since measured amounts of antalarmin were administered to the rats (see Figure 1, p. 5748), the limitations of kits (claims 13-14) are also met. Thus claims 4-10 and 13-14 do not teach anything new over the prior art.

The rejection of claims 4-7, 9-10 and 13-14 under 35 U.S.C. 102(b) as being anticipated by Habib et al. (PNAS, 2000; 97: 6079-6084) as set forth at pages 3-5 of the Office action mailed 22 January 2008 is maintained for reasons of record and the following.

Applicants argue at p. 13, 3rd paragraph that Habib does not teach a pharmaceutical composition or kit for treating an inflammatory disease using CRH-R1 antagonists and/or CRH-R2 agonists, wherein the CRH-R1 antagonists and/or CRH-R2 agonists directly modify the response of monocyte/macrophage cell activation, proliferation, differentiation or apoptosis.

This argument has been fully considered but is not found persuasive.

The claims are drawn to a pharmaceutical composition, which is a ***product***. See In re Papesch, 315 F.2d 381, 391, 137 USPQ 43, 51: "From the standpoint of patent law, a compound and all its properties are inseparable." Note that the recitation, "directly modifying the response of monocyte/macrophage cell activation, proliferation, differentiation or apoptosis" is given little patentable weight for the purpose of evaluating the prior art, because it does not further limit ***the structure of the product***. Habib teach oral administration of antalarmin (a CRH-R1 antagonist) dissolved in Primatreat banana flavored tablet form to primates (see p. 6080, left column, 3rd – 4th paragraphs), and since the antalarmin was found to have an anxiolytic therapeutic effect (see

abstract; p. 6084, right column, last paragraph), this usage is consistent with pharmaceutical use, thus meeting the limitations of claims 4, 5, 6, 7, 9 and 10. Because the antalarmin was formulated for oral dosage, and measured amounts were given (see 6080, left column, 4th paragraph), the claims also meet the limitations of a kit (claims 13 and 14). Because the product taught by Habib and colleagues is identical to that taught in the instant application, the prior art product must, by definition, have the same ability to directly modify the response of monocyte/macrophage cell activation, proliferation, differentiation or apoptosis. It is not necessary for Habib et al. to have disclosed the mechanism of action, as the claims are drawn to products and Habib et al. disclose the identical products and their usefulness in therapy, thus the usage taught by Habib and colleagues is consistent with a pharmaceutical composition. Thus claims 4-7, 9-10 and 13-14 do not teach anything new over the prior art.

The rejection of claims 4-8 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Wei et al. (Peptides, 1998; 19: 1183-1190) as set forth at pages 10-11 of the Office action mailed 22 January 2008 is maintained for reasons of record and the following.

Applicants argue at p. 14, 1st paragraph that Wei et al. do not describe synthetic CRH-R1 and CRH-42 but rather cells transfected with CRH1 or CRH2β.

The Examiner does not agree with this characterization. The title of the paper by Wei et al. is: "D-Amino Acid-substituted Analogs of Corticotropin-releasing Hormone and Urocortin with Selective Agonist Activity at CRH1 and CRH2β ***Receptors***." (Emphasis Added). Wei et al. teach synthetic D-amino acid-substituted peptides with

selective CRH receptor agonist activity (see whole document, for example, abstract; p. 1187, Table 2; p. 1189, right column, last paragraph).

Applicants argue at p. 14, 1st paragraph that Wei et al. do not teach a pharmaceutical composition or kit for treating an inflammatory disease using CRH-R1 antagonists and/or CRH-R2 agonists, wherein the CRH-R1 antagonists and/or CRH-R2 agonists directly modify the response of monocyte/macrophage cell activation, proliferation, differentiation or apoptosis.

This argument has been fully considered but is not found persuasive. The claims are drawn to a pharmaceutical composition, which is a ***product***. See In re Papesch, 315 F.2d 381, 391, 137 USPQ 43, 51: "From the standpoint of patent law, a compound and all its properties are inseparable." Note that the recitation, "directly modifying the response of monocyte/macrophage cell activation, proliferation, differentiation or apoptosis" is given little patentable weight for the purpose of evaluating the prior art, because it does not further limit ***the structure of the product***. Because the product taught by Wei and colleagues has CRH-R2 agonist activity, which meets the limitation of the claims, the prior art product must, by definition, have the same ability to directly modify the response of monocyte/macrophage cell activation, proliferation, differentiation or apoptosis. Possible therapeutic applications are discussed at p. 1184, right column, 1st paragraph, thus the usage taught in Wei et al. is consistent with pharmaceutical usage. In addition, Wei et al. teach administration of measured amounts (for example Table 2, Figures 2-5), the limitations of a kit is also met. It is not necessary for Wei et al. to have disclosed the mechanism of action, as the claims are drawn to products and Wei et al. disclose a product and its possible use as a

therapeutic agent, thus the usage taught by Wei and colleagues is consistent with a pharmaceutical composition. Thus claims 4-8 and 13 are anticipated by Wei et al.

At pages 14-16, Applicants make arguments regarding the non-obviousness of their invention over the cited prior art. The Examiner did not make any rejections under 35 U.S.C. 103(a), which pertains to obviousness, thus these arguments are not relevant to the standing rejections and will not be addressed.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is (571)272-4482. The examiner can normally be reached on 8:00am - 2:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christina Borgeest, Ph.D.

/Elizabeth C. Kemmerer/

Primary Examiner, Art Unit 1646